Claim 8, which originally depended from claim 7, has been amended to depend from claim 1 in view of the cancelation of claim 7, and to replace the term "modulator" with the term "compound";

Claims 9, 12, 13 and 15, which originally depended from claim 7, have been amended to depend from Claim 8 in view of the cancelation of claim 7;

Claim 16 has been amended to recite that the "growth factor receptor" is effected by the compound in order to properly depend from claim 1;

Claim 17 has been amended into a method claim for treating growth-factor receptor-associated disorders according to the method of claim 1;

Claim 18 now recites that the "disorder" is cancer or asthma;

Claim 19 has been amended to depend from claim 17, and to recite that an effective amount of the compound is used to treat the subject;

Claim 20 has been amended into a method for screening compounds; and

Claim 21, which depends from claim 17, recites an embodiment for the type of disorder to be treated.

No new matter has been added to the amended claims, and consideration and entry of the amended claims is requested.

I. Response to Objection to Drawings

The drawings have been objected to by the draftsperson, and once any claims have been allowed, Applicants will submit formal drawings.

II. Response to Rejection of Claims 1, 17, 18 and 21 under 35 U.S.C. §112, first paragraph

Claims 1, 17, 18 and 21 are rejected under 35 U.S.C. §112, first paragraph, for lack of enablement.

For purposes of brevity, Applicants incorporate by reference, the Examiner's comments set forth in the Office Action.

Applicants traverse as follows.

The arguments set forth in the response of August 3, 2001 are respectfully incorporated herein in their entirety, and Applicants reassert that the claims are fully enabled.

As proof of the in vivo applicability of the method according to the invention for the treatment of heart diseases, Applicants are enclosing a copy of a recent publication by Asakura et al. (Nature Medicine 8 (2002), 35-40) and the accompanying article by Liao. From these publications, it is readily apparent that a heart disease can be caused by a hypertrophic process mediated by signaling through G-protein coupled receptors (GPCRs). The signal produced from GPCR is in turn transduced to the EGFR via a metalloprotease (ADAM12) and cleavage of the membrane-bound GB-EGF. This is exactly the same means of signal transduction disclosed in the present application, and substantiates the therapeutic applicability of the subject matter of the present invention.

Accordingly, claims 1, 17, 18 and 21 meet the statutory requirements for enablement under §112, first paragraph, and withdrawal of the rejection is deemed proper.

III. Response to Rejection of Claims 1, 3-6, 16, 19 and 20 under 35 U.S.C. §102(b)

Claims 1, 3-6, 16, 19 and 20 are rejected under 35 U.S.C. §102 as being anticipated by Daub et al. (EMBO.J. 16, 7032-7044, December 1997).

For purposes of brevity, Applicants incorporate by reference, the Examiner's comments set forth in the Office Action.

Applicants traverse for the following reasons.

Daub describes a connection between G-protein coupled receptor and growth-factor receptor, e.g. EGFR. However, according to this publication, the activation of EGFR does not occur though the extracellular domain, but through an intracellular signal. In view of Daub, Applicants submit that the instant invention is both novel and nonobvious since Daub does not teach or suggest using a metalloproteinase or a ligand precursor of the growth-factor receptor, respectively, as therapeutical targets for influencing this cascade. Applicants were the first to demonstrate that these components are able to activate EGFR via the extracellular domain. Applicants have made the unexpected discovery that a signal cascade caused by a disorder associated with the G-protein or the GPCR, can be interrupted by inhibiting the metalloproteinase or the release of the ligand precursor, respectively. Based on the teaching of Daub, one skilled in the art would not have expected that the metalloproteinase or the ligand precursor, respectively, would be suitable targets for a therapeutic treatment of G-protein/GPCR associated disorders. Accordingly, Daub teaches away from the subject matter of the instant claims.

IV. Response to Rejections of Claims 1, 3-16, 19 and 20 under 35 U.S.C. §102(a)

Claims 1, 3-16, 19 and 20 are rejected under 35 U.S.C. §102(a) as being anticipated by Dong et al. (Proc. Natl. Acad. Sci. USA, 96, 6235-6240, May 1999).

For purposes of brevity, Applicants incorporate by reference, the Examiner's comments set forth in the Office Action.

Applicants traverse for the following reasons.

Dong discloses that a metalloproteinase mediated ligand release regulates autocrine signaling through the epidermal growth-factor receptor. Dong teaches that inhibition of the metalloproteinase prevents cleavage of the ligand precursor and thus ligand release, which leads to deactivation of EGFR. Dong is specifically silent that the instantly claimed therapeutic approach can be applied in the modulation of disorders associated with the G-protein of the GPCR.

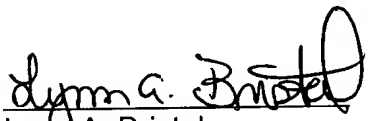
Accordingly, the claims do not read on, and therefore are not anticipated by Dong. Withdrawal of the rejection is deemed proper.

CONCLUSION

Applicants submit that in view of the foregoing amended claims and all of the foregoing arguments, the Examiner's rejections of the claims under 35 U.S.C. §§102(a), 102(b) and 112, first paragraph, have been met and overcome. Applicants submit that the application is now in condition for allowance, and request that the Examiner pass the application to issuance.

Please charge any fee deficiency or credit any overpayment to Deposit Account No. 01-2300.

Respectfully submitted,



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1.(Twice Amended) A method for modulating growth-factor receptor activation by G-protein-mediated signal transduction, comprising contacting a cell or an organism [which contains] containing a growth-factor receptor capable of [being activated with a modulator of] activation by G-protein mediated signal transduction [, so as to activate the growth-factor receptor, wherein said activation of the growth-factor receptor is mediated] by its extracellular domain, with a compound effecting a proteinase and/or a ligand precursor for the growth-factor receptor.

3. (Twice Amended) The method of claim 1, wherein the activation of the growth-factor receptor is mediated [via] by an extracellular signal pathway.

8. (Amended) The method of claim [7] 1, wherein [said modulator acts on said] the compound effects the proteinase by directly stimulating or inhibiting [the] proteinase activity.

9. (Twice Amended) The method of claim [7] 8, wherein said proteinase cleaves a growth-factor precursor.

11. (Twice Amended) The method of claim 9, wherein said growth factor ligand precursor is [proHB-EGF] proheparin-epidermal growth factor (proHB-EGF) and said growth-factor receptor is EGFR.

12. (Twice Amended) The method of claim [7] 8, wherein said proteinase is a membrane-associated proteinase.

13. (Twice Amended) The method of claim [7] 8, wherein said proteinase is a metalloproteinase.

15. (Twice Amended) The method of claim [7] 8, wherein said proteinase activity is inhibited by batimastat.

16. (Twice Amended) The method of claim 1, wherein said [modulator acts on] compound effects a cell which is different from the cell [which contains] containing the growth-factor receptor.

17. (Twice Amended) [The] A method [of claim 1] for [the prevention or treatment of disorders] treating a subject with a disorder associated with or accompanied by a disturbed growth factor receptor activation by G-protein mediated signal transduction, said method comprising modulating in the subject in need thereof, the growth receptor activation according claim 1.

18. (Twice Amended) The method of claim 17, [for the treatment of] wherein the disorder is cancer or asthma.

19. (Twice Amended) The method of claim [1] 17, wherein [said modulator] a growth-factor receptor-modulating effective amount of the compound is administered [as a pharmaceutical composition] to the subject in need thereof.

20. (Amended) A method for identifying [and providing modulators] compounds for modulating growth-factor receptor activation by G-protein mediated signal transduction, comprising contacting a cell [which contains] containing a growth-factor receptor capable of [being activated] activation by G-protein mediated signal transduction with a test compound suspected [to be] of being a modulator of [G-protein mediated signal transduction] of a proteinase or a ligand precursor of the growth factor receptor, and [determining the degree of] evaluating G-protein mediated growth-factor receptor activation upon exposure of the cell to the test compound.

21. (Amended) The method of claim 17, [for the prevention or treatment of disorders associated with or accompanied by] wherein the disturbed growth factor receptor activation is a pathologically enhanced growth receptor activation.